Institution: University of Birmingham

Unit of Assessment: 5 – Biological Sciences

Title of case study: Establishing a supply chain for a revolutionary new reagent for the global pharmaceutical industry

Period when the underpinning research was undertaken: January 2009–December 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor T. Dafforn	Professor	15/12/2003–present
Professor M. Overduin	Professor	01/09/2002–31/07/2015
Dr Tim Knowles	Lecturer	10/01/2005–present

Period when the claimed impact occurred: June 2016 -– December 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Dafforn and team have **contributed to innovation and entrepreneurial activity by designing and bringing to market new products and services** in the form of the Styrene Maleic Acid Lipid Particle **(SMALP)** method which is used in the production of membrane proteins. The SMALP method performs significantly better than previous approaches, transforming the speed, efficiency and cost of the drug discovery process. The approach was **licensed to a new business** to enable the supply of SMALP products directly to the global pharmaceutical sector. Further innovation was enabled from the **development of new services** by contract manufacturers who have increased the efficient supply of membrane proteins to pharmaceutical companies, further accelerating the drug discovery process.

2. Underpinning research (indicative maximum 500 words)

Membrane proteins comprise >60% of new and existing drug targets, making them the most economically important class of proteins for the pharmaceutical industry. Just one class of membrane proteins, GPCRs, accounts for 27% of the global market share of therapeutic drugs, with aggregated sales for 2011–2015 of ~US$890 billion. However, *membrane proteins are also exceptionally challenging and expensive to produce at scale*. Existing production methods are based on the use of detergent and yield membrane proteins with low stability and low activity. Low yield and high cost are long acknowledged to be major factors limiting the development of new drugs.

In 2009, University of Birmingham (UoB) research, funded by research councils and industry, led to the development of the **Styrene Maleic Acid Lipid Particle (SMALP)** method for use in the production of membrane proteins [R1, R2]. This new and innovative method represented a step-change in the process of membrane proteins production overcoming many limitations of previous production methods. The patent for the SMALP process was granted to UoB in 2014 (8754168) prior to the publication of the full method [R2]. Key findings of the SMALP method are as follows:

KF1: **The SMALP process boosts the yield of some membrane proteins up to 10-fold.** This means proteins that were previously intractable due to their low abundance are now available for biochemical and pharmaceutical studies [R1].

KF2: Proteins within SMALPs have **significantly enhanced stability compared to detergent extractions**. The stabilised proteins can also be used in drug binding assays at physiological temperatures which is important in cases where such experiments need to closely mimic conditions in the patient — working at such elevated temperatures is often impossible for detergent based samples [R3].

KF3: Unlike detergent prepared samples, proteins in SMALPs can be stored for long periods as either a dry powder or frozen at -70°C. This allows a **single preparation to be used for multiple drug discovery campaigns** over a long period of time. Detergent solubilised samples often have to be remade each time they are used increasing the variability of the drug discovery process [R3].

KF4: **Proteins in SMALPs are compatible with a wide range of drug binding assays** (e.g. Radioligand binding assays, SPR, Fluorescence binding assays) commonly used by the pharmaceutical industry. This means that they are commercially highly desirable [R3–R5].

KF5: The **SMALP method is generically applicable** to most membrane protein families that are the subject of drug discovery campaigns including G-protein coupled receptors, ion channels and ABC-transporters [R3–R5].

3. References to the research (indicative maximum of six references)

R1: Knowles TJ, Finka R, Smith C, Lin YP, Dafforn TR, Overduin M. 2009, Membrane proteins solubilized intact in lipid containing nanoparticles bounded by styrene maleic acid copolymer. J Am Chem Soc, 131(22):7484-5. DOI: 10.1021/ja810046q

R2: Lee SC, Knowles TJ, Postis VL, Jamshad M, Parslow RA, Lin YP, Goldman A, Sridhar P, Overduin M, Muench SP, Dafforn TR. 2016, A method for detergent-free isolation of membrane proteins in their local lipid environment. Nat Protoc, 11(7):1149-62. DOI: 10.1038/nprot.2016.070

R3: Jamshad M, Charlton J, Lin YP, Routledge SJ, Bawa Z, Knowles TJ, Overduin M, Dekker N, Dafforn TR, Bill RM, Poyner DR, Wheatley M 2015, G-protein coupled receptor solubilization and purification for biophysical analysis and functional studies, in the total absence of detergent. Biosci Rep, 35(2):e00188. DOI: 10.1042/BSR20140171

R4: Gulati S., Jamshad M, Knowles TJ, Morrison KA, Downing R, Cant N, Collins R, Koenderink JB, Ford RC, Overduin M, Kerr ID, Dafforn TR, Rothnie AJ 2014, Detergent-free purification of ABC (ATP-binding-cassette) transporters. Biochem J, 461(2):269-78. DOI: 10.1042/BJ20131477

R5: Dörr JM, Koorengevel MC, Schäfer M, Prokofyev AV, Scheidelaar S, van der Cruijsen EA, Dafforn TR, Baldus M, Killian JA 2014, Detergent-free isolation, characterization, and functional reconstitution of a tetrameric K+ channel: the power of native nanodiscs. Proc Natl Acad Sci U S A ,111(52):18607-12. DOI: 10.1073/pnas.1416205112

4. Details of the impact (indicative maximum 750 words)

The patented SMALP method [KF1–KF5] has made a significant **contribution to innovation and entrepreneurial activity**. The method was rapidly adopted (<2 years) by the global pharmaceutical sector and has impacted **all levels in the commercial drug discovery supply chain** (summarised in Figure 1). The research has directly and materially transformed each stage of the supply chain; **from licence, to new businesses and product development, to globally improving productivity and to improving the businesses of contract manufacturers**. Taken together, research-led changes in production are contributing to reducing the costs of future drug treatments/therapeutics.

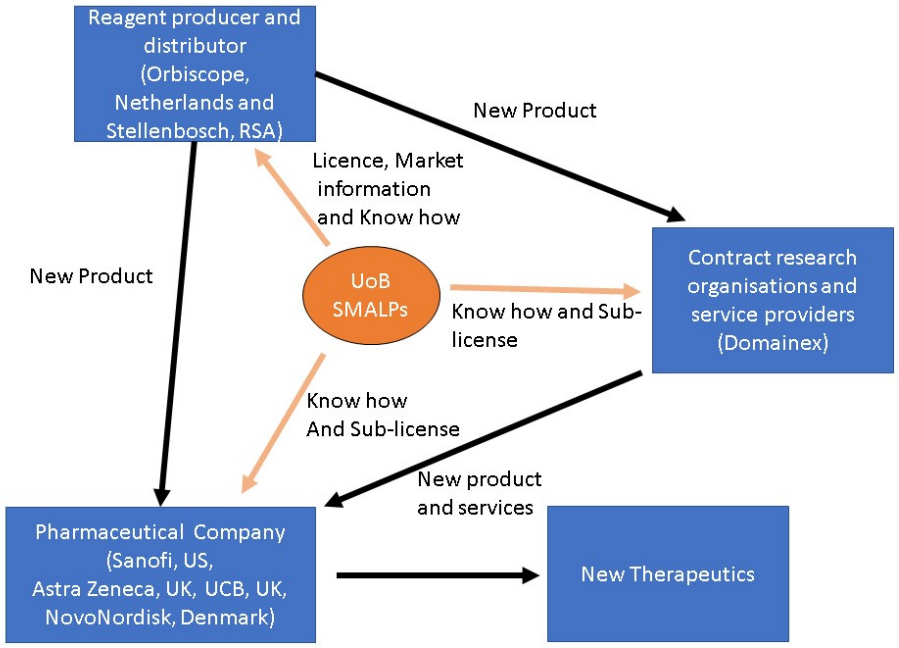

Figure 1: Schematic showing the flow of research findings across the drug discovery supply chain.

Contribution to entrepreneurial activity by licensing and bringing to market the SMALP method

The SMALP method was commercialised though the **award of an exclusive licence** (based on the patent utilising KF1–KF4) from the University of Birmingham to Polyscope Polymers BV in the Netherlands, the global leaders in the production of Styrene Maleic Anhydride (SMA). Upon acquisition of the license [EV1], **a new business was created** by Polyscope — *Orbiscope*, with the unique function to globally commercialise SMALPs.

The **demonstrable collaboration** between the University of Birmingham and Orbiscope developed rapidly, leading to the **design, delivery and adoption of two further variants of SMALP as new products** (SMI and DIBMA). Just the first year of trading (2020) saw the creation of two **new jobs** in the new business with **material sales** yielding revenues of >£100K. The Business Unit Manager of Orbiscope stated:

> In 2018 we became aware of Professor Dafforn's pioneering work using our polymers in the production of membrane protein drug targets. We recognised that this could be a significant opportunity for Polyscope and agreed a global exclusive licence with the University of Birmingham in 2019. Since 2019 we have employed Professor Dafforn as a consultant and with his assistance we launched a new business unit, Orbiscope, in 2020 to support the commercialisation of SMA polymers for pharmaceutical applications. Without the support of Professor Dafforn it is highly unlikely that we would have launched this new business [EV2].

This work led to an agreement between Orbiscope and Stellenbosch to develop a new **manufacturing facility** for the DIBMA product in South Africa [EV3]. Further partnerships with two businesses (Cube Biotech and Sigma-Aldrich) have provided a global distribution network for the polymers [EV4].

Contribution to innovation through take up of new SMALP products and process in the global pharmaceutical sector

The SMALP method and products have been integrated into the working process of pharmaceutical industries in the UK, US and Europe where it is **increasing the success and productivity of the drug discovery process**, in addition to **reducing costs**. This high rate of adoption was due to Dafforn and his team priming the global pharmaceutical sector (e.g. Sanofi, UCB Pharma, Novonordisk, Astrazneca etc) prior to the award of the license to Polyscope.

As an example, in a **demonstrable collaboration** between UoB and the global pharmaceutical sector, Dafforn highlighted the utility of the SMALPS method to Sanofi (USA and Germany) in a commercial setting. The now general availability of SMALPS has enabled Sanofi to reduce the cost of production of one of their targets while allowing another to be produced that had previously been intractable, as testified by a former drug discovery scientist at Sanofi:

> […] we worked together to apply your method to 3 targets (one of which was with one of our laboratories in Germany). In each case your SMALP method succeeded where conventional methods had failed. This meant that your SMALP method allowed us to realise a significant productivity improvement within our drug discovery pipeline. To give some context, one of the targets that you successfully managed to produce in less than 1 week, had been the focus of a much larger project that had cost >$1 million and failed to yield significant amounts of the protein target. On this basis alone it is clear that your SMALP method also provides significant cost reductions for the drug discovery industry [EV5].

Enabling contract manufacturers to launch new services based on the SMALP method

The increased use of SMALP by the global pharmaceutical business has provided an additional commercial opportunity in the middle of the supply chain. Entrepreneurial contract manufacturing companies have **launched new products and services** to further support the drug discovery effort.

For example, in the UK, **the performance of an existing business, Domainex, has been improved** through the introduction of new SMALP based services derived from Orbiscope products. After identifying membrane protein production as an opportunity for growth, UoB were approached by drug discovery service company Domainex to integrate the SMALP system into their business. Following a successful Innovate UK funded trial, Domainex launched a new receptor purifying service [EV6, EV7] to pharmaceutical companies based on SMALPs. Domainex now supply two US based biotech companies and a European research institute [EV8], as testified by the team leader in Assay Biology at Domainex:

> Prior to working with Professor Dafforn our business was mainly based on early stage drug discovery for targets that were soluble proteins. It became increasingly clear to us that we needed to extend our business to also encompass membrane proteins [i.e. SMALP…] we were able launch an entirely new service, PoLiPa, at Discovery on Target in Boston in 2018 based on Professor Dafforn's SMALP technology. Having the potential to be transformative in the field, this has generated an unprecedented level of business interest for the company and is already beginning to lead to new contracts utilising the technology [EV7].

5. Sources to corroborate the impact (indicative maximum of 10 references)

EV1: License agreement between University of Birmingham and Polyscope Polymers

EV2: Testimonial from Orbiscope

EV3: DIBMA production evidence [Dated 19 January 2021]

EV4: Link to Cube Biotech outlining their SMA and DIBMA offering [Accessed 3 March 2021]

EV5: Testimonial from former scientist at Sanofi detailing the importance of integrating the SMALP method into their processes

EV6: Link to Domainex website outlining their SMALP offering [Accessed 3 March 2021]

EV7: Testimonial from Domainex detailing the changes in business practice induced by adoption of method [Dated 26 October 2020]

EV8: Email from Domainex outlining state of play of the business at the end of the REF assessment period